IRB • SPONSOR ROUNDTABLE

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US Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2005N-0038
Reporting of Adverse Events to Institutional Review Boards

These comments are submitted on behalf of the IRB-Sponsor Roundtable ("the Roundtable") in response to the FDA's request set forth in 70 Federal Register 6693 (February 8, 2005; ***Reporting of Adverse Events to Institutional Review Boards; Public Hearing***), and supplement the Roundtable's statement at the March 21, 2005 FDA public hearing on this topic.

I. BACKGROUND

The IRB-Sponsor Roundtable is comprised of individuals affiliated with Institutional Review Boards (IRBs)[1] and representatives of pharmaceutical companies that sponsor clinical research.[2] The Roundtable's mission is to facilitate constructive communication between sponsors and IRBs on significant, overarching clinical research issues and, where possible, (i) propose practical strategies for improving clinical trials process and human subject protections, and (ii) engage other affected stakeholders in the clinical research community to

[1] Throughout these comments all references to IRBs are meant to include both central IRBs and individual institutional IRBs.

[2] The current participants in the Roundtable are: Novartis Pharmaceuticals; Pfizer Inc.; Sanofi-Aventis; Schering-Plough; Marianne Elliott, US Navy; Dr. Felix Gyi, Chesapeake Research Review, Inc.; Karen Hansen, Fred Hutchinson Cancer Research Center; John Isidor, Schulman Associates IRB, Inc.; Moira Keane, University of Minnesota; Dan Nelson, UNC Chapel Hill; Dr. Pearl O'Rourke, Partners Healthcare System; Dr. Ernie Prentice, University of Nebraska Medical Center; and Ada Sue Selwitz, University of Kentucky.

promote broader dialogue and consensus building. The Roundtable's principal objective is to enhance the protection of human subjects.

The Roundtable views the current challenges associated with the process of adverse event ("AE") reporting in multi-site trials as a priority, and commends FDA for seeking input from interested stakeholders on this topic. As detailed herein, the Roundtable believes that it is essential to establish a new model for AE reporting that will: (i) promote responsible and effective AE reporting through a multi-party process that includes appropriate checks and balances, and reinforces the active participation of IRBs, principal investigators, sponsors, and, where relevant, data monitoring bodies[3] in identifying potential risks for subjects, and (ii) enhance the protection of human subjects by ensuring the medically and scientifically relevant data on AEs is communicated to IRBs in a meaningful way, in particular highlighting those AEs that are likely to negatively impact the risk profile in a clinical trial. Definitions of key terms referenced in this Submission are contained in Appendix A.

II. BRIEF STATEMENT OF PROBLEM

The Roundtable generally concurs with the description of the issues and challenges related to AE reporting in multi-site trials as set forth in ***Section I (Background)*** of the February 8, 2005 Federal Register Notice and detailed during presentations at the public hearing on March 21, 2005. Based on the views expressed during the March hearing, it appears that a broad consensus exists regarding the need for FDA and other interested agencies to address these issues as a priority, in collaboration with IRBs, investigators, sponsors of clinical research and other interested stakeholders. We wish to highlight the following points:

- Increasingly, a clinical study of an investigational drug is conducted at numerous sites across the United States and around the world; these large multi-site studies include thousands of human subjects. Each study site is usually overseen by a different IRB charged with ensuring that risks are minimized for study participants at that site.[4]

- The existing regulatory framework was developed before multi-site trials were commonplace. The traditional AE reporting approach used

[3] For example, Data Safety Monitoring Boards (DSMB) or Data Safety Committees (DMC).
[4] If an independent / central IRB is involved they will oversee numerous sites.

successfully in single-site studies is not well-suited to today's multi-site study model.

- The regulatory definitions and processes for AE reporting differ among FDA and other agencies leading to some confusion and varying interpretations.

- The sheer volume and disaggregated nature of AE reports make it difficult for IRBs and principal investigators to effectively evaluate their significance and the implications for study subjects. The primary objective of collecting and analyzing AE reports in multi-site trials is to protect human subjects by continuously monitoring the risk/safety profile to ensure that the profile continues to be acceptable. In order to make educated, timely judgments about the risk/safety profile, IRBs and principal investigators would benefit from more coordinated, distilled information about AEs that occur within the context of multi-site trials.

III. COMMENTS ON FDA'S "ISSUES FOR DISCUSSION" (70 FED. REG. AT 6694-6695)

A. The Role of IRBs in the Review of Adverse Event Information from Ongoing Clinical Trials

- ***What role should IRBs play in the review of adverse events information from an ongoing trial?***
- ***How does the role differ from the current role of IRBs?***
- ***Should IRB responsibilities for multi-site trials differ from those for single-site trials? If so, how should they differ?***

At the outset, it is important to note that the term "adverse events" is not used in the regulatory requirements applicable to IRBs. Pursuant to 21 CFR § 56.108(b), IRBs must have written procedures in place to ensure prompt reporting to the IRB, appropriate institutional officials, and FDA of any "unanticipated problems involving risks to human subjects or others." This phrase is generally undefined and could be interpreted as requiring reporting of any risks, even very minor ones. IRBs are also responsible for conducting "continuing review" of ongoing clinical trials at "appropriate intervals," at a minimum annually. (21 CFR § 56.109(f)).

Different terms and regulatory definitions are used when describing the obligations of the other key stakeholders in the clinical research process –

sponsors and investigators. Sponsors must report to FDA and all investigators "any adverse experience associated with use of the drug that is both serious and unexpected."[5] Investigators are required to report to the sponsor "any adverse event that may reasonably be regarded as caused by, or probably caused by, the drug;" any "alarming" effects must be reported immediately.[6] The rationale, if any, for these varying terms and regulatory standards is unclear. The Roundtable encourages FDA to collaborate with other interested agencies (***e.g.,*** OHRP) to clarify these definitions and, where possible, promote uniformity, consistent with the recommendations below.

FDA has posed the question of the IRB's role in the "review" of AEs. The Roundtable believes that it is important for IRBs to be ***informed*** throughout the trial of anything that negatively impacts the risk profile and, in particular, any AE, or group of AEs, that would require modification of the study protocol and/or revisions to the informed consent form. This is critical to promoting the IRB's central role in protecting human subjects throughout the trial. However, it is important to note that IRBs are not intended to function as safety oversight committees (***e.g.,*** Data Safety Monitoring Boards [DSMB]) and, indeed, are not constituted to serve in that capacity. In multi-site studies, IRBs generally do not have access to the type of relevant information necessary to effectively evaluate disaggregated AE reports and put them into the proper context to determine what is scientifically and medically relevant – the type of activities that would constitute a substantive, meaningful ***review*** of AEs. Currently, IRBs receive an overwhelming number of individual AEs on an ad hoc basis throughout the trial. While IRBs frequently attempt to read and understand each individual AE, the "signal to noise" ratio is now unfavorably dominated by noise making it difficult, if not impossible, for IRBs to play a real role in ***reviewing*** individual reports of AEs.

Based upon the input provided during the March 21, 2005 FDA hearing, and initial outreach to principal investigators conducted by the Roundtable, it appears that principal investigators face similar challenges in responding to the voluminous, disaggregated flow of AE reports. Therefore, the Roundtable's recommendations at pages 7-9 suggest that the model for AE reporting be revised for both IRBs and principal investigators. We recognize that this will

[5] 21 CFR § 312.32(c)(1)(i). Under the regulations, "associated with the use of the drug" means that there is a "reasonable possibility that the experience may have been caused by the drug."
[6] 21 CFR § 312.64(b).

require revising the existing regulatory framework, in addition to official guidance from FDA and other interested agencies.

As detailed below, the Roundtable recommends that the current practice of sending individual AE reports to IRBs and principal investigators throughout the trial, without any context or recommended action, be eliminated in favor of establishing processes and procedures requiring the sponsor (in conjunction with the DMSB for the study, if there is one) to provide IRBs and investigators, at appropriate intervals, with a summary report of the evolving safety profile in the study, including a listing of individual expedited AE reports (unblinded, if appropriate) that were submitted to regulatory authorities during the reporting period. The summary report would provide clear recommendations for actions that should be taken in response to AEs that have occurred during the trial, through that period of time (***e.g.,*** modification to protocol; revision to informed consent; or halting of trial).

When conducting initial review of a potential clinical trial, the IRB has an important role to play in reviewing the data safety communication plan prepared by the sponsor and included in the study protocol. The potential elements of the data safety communication plan are detailed at pages 7-8.

B. The Types of Adverse Events About Which IRBs Should Receive Information

- ***Based on your view of the role of IRBs in the review of adverse event information from ongoing clinical trials, what types of adverse events should an IRB receive information about, and what types of information need not be provided to IRBs?***
- ***In a multicenter study, should the criteria for reporting adverse events differ, depending on whether the adverse events occur at the IRB's site or at another site?***

As discussed above, it is counterproductive for IRBs and principal investigators to receive an ongoing "stream" of individual AE reports without meaningful interpretation conducted by the sponsor and / or DSMB.

The Roundtable recommends that the reporting of AEs should differ depending on whether the AE is "internal" or "external."[7] IRBs have an increased responsibility over the subjects enrolled at their own institution and

[7] ***See*** Appendix A for definitions of key terms.

are better able to obtain sufficient information from the principal investigator to successfully evaluate the significance of these internal (sometimes referred to as "local") AE reports. Further, if the IRB is receiving more coherent information on external AE reports via periodic summary reports (described below), rather than being inundated with individual reports, they will be better able to manage internal AE reports.

C. Approaches to Providing Adverse Events Information to IRBs

- ***What can be done to provide IRBs adverse event information that will enable them to better assess the implications of reported events for study subjects?***
- ***When should consolidated reports be provided to IRBs (e.g., at specified intervals, only when there is a change to the protocol, informed consent, or investigator's brochure due to adverse event experience)? Who should provide such reports?***

In order to better assess the implications of AEs that occur during a clinical study, the IRB needs to receive timely information about AEs in a coherent, logical, and consistent format that provides the context for understanding how the safety profile is evolving and, wherever possible, makes recommendations regarding what action (if any) should be taken. This type of distilled and targeted information will facilitate the IRB's overarching responsibility to ensure that the rights and wellbeing of research subjects are protected throughout the trial. The Roundtable believes that this can be accomplished if FDA, ideally in collaboration with OHRP and other interested agencies, issues guidance and, where necessary, revises the existing regulatory framework to establish a new paradigm for AE reporting in multi-site trials that is workable, effective, and better promotes the safety of human subjects.

Specifically, the Roundtable recommends the following:

- In the study protocol submitted to IRBs for review and approval, the sponsor should clearly articulate a data safety communication plan for providing safety information to IRBs and principal investigators. A core aspect of the data safety communication plan will be periodic summary reports providing a qualitative assessment of all of the safety information relevant to the trial, including all expedited AEs and other safety information. The safety communication plan should be developed and implemented in a flexible manner to meet the specific needs of the clinical trial, but will likely include one or more of the following elements:

- a proposed schedule for timely submission of aggregate safety information in a summary report (***e.g.,*** quarterly, semi-annually, or annually) to the IRBs and principal investigators. Quarterly reports will likely be suitable in many clinical studies, but a more or less frequent reporting schedule could be necessary in some types of studies. The sponsor, investigators and IRBs will carefully consider at the outset of the trial the most appropriate frequency of the aggregate summary reports depending on the needs and risks of the study. As noted below, if an immediate safety risk is identified, "ad hoc" safety information would be submitted on an expedited basis;

- the proposed content and format for the submission of periodic summary reports. The summary reports should include a line listing of all expedited AEs (unblinded, if appropriate[8]) and highlight any AE or series of AEs that require modification of the study protocol or revision of the informed consent;

- a description of the functioning of a DSMB, if applicable, as well as the method and frequency of communication of DSMB reviews to investigators and IRBs[9];

- the criteria and a process for determining when individual AE reports should be communicated to the IRB and principal investigator on an expedited basis. For example, if a single AE requires modification of the study protocol, revisions to the informed consent, or is reflective of some other major concern impacting the study, the sponsor should notify the principal investigator promptly and the investigator should provide the AE report to the IRB as soon

[8] The data safety communication plan should include a discussion of whether and when it would be possible to use unblinded data.

[9] DSMBs are typically required in Phase III and Phase IV trials, and may sometimes be appropriate for Phase I or Phase II trials. ***See, e.g.,*** Guidance from the National Institute of Health: ***Further Guidance on Data Safety and Monitoring*** (June 5, 2000); Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials (June 22, 1999).

as possible thereafter[10] with the recommended action clearly noted;[11] and

- guidelines for when the trial should be discontinued or altered (often referred to as "stopping rules").

- The periodic aggregate summary safety reports should be prepared by the sponsor (in coordination with the DSMB, if applicable). The sponsor will circulate the summary report to all principal investigators involved in the clinical study, and the principal investigator will review the reports and provide them to the local IRB. The sponsor will document its analysis of all expedited AE reports and this analysis will be subject to audit by the IRB (or their designated compliance arm) and FDA.

- The following best practices should be implemented: (i) if the sponsor concludes that an external AE report warrants immediate referral to all IRBs, it should highlight the report to the principal investigators and provide a rationale for expedited transmission to all IRBs; (ii) a principal investigator should provide any external AE reports to the IRB that they believe warrant immediate attention (***i.e.,*** modification of the protocol, revision to the informed consent, or other major concern impacting the study such as suspension of local accrual), even if the sponsor has not highlighted them as such, provided that they state the rationale for transmission of the AE report(s); and (iii) when a sponsor becomes aware that one of the IRBs in a multi-site study has required a significant action be undertaken (***e.g.,*** modification of protocol, revisions to informed consent, or halting of trial), the sponsor should notify all principal investigators and direct the investigators to provide notice to all of the IRBs involved in the trial. These best practices are already being used in some contexts, but it is important to ensure that they are outlined in the data safety communication plan and followed broadly and consistently.

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[10] The timeframes for transmission from the sponsor to the investigator, and then from investigator to IRB should be clearly specified in the safety communication plan so that all parties are aware of the requirements. These timeframes should be consistent with existing regulatory requirements, as appropriate. For example, FDA's IND regulations require that any AE that is serious, unexpected and associated with the use of the drug be reported to FDA within 15 calendar days after the sponsor's initial receipt of the information.

[11] If the AE results in death or a life-threatening experience, it will likely be appropriate for transmission on an expedited ad hoc basis.

IV. CONCLUSIONS

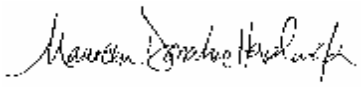
The IRB-Sponsor Roundtable believes that the current wide-spread practice of sending individual external AE reports to all IRBs and principal investigators in a multi-site study is ineffective, counterproductive, and inconsistent with the core objective of promoting the safety of human subjects participating in clinical trials. As detailed in this Submission, the Roundtable recommends that a new paradigm be adopted whereby the IRBs and investigators in a multi-site trial will receive periodic aggregate summary reports of safety information that provide meaningful context and, wherever possible, include practical concrete recommendations on any necessary follow up actions. Individual external AE reports should only be submitted on an ad hoc basis when necessary to protect human subjects.

While best practices are now employed in some contexts to help ensure that IRBs and investigators receive comprehensive, meaningful information about the evolving safety profile in a study, these practices should be adopted across the clinical research enterprise. To achieve this important goal, it is essential for FDA and other interested agencies to issue official guidance and, in some instances, revise the existing regulatory framework, to clearly articulate a coherent process for collecting and reporting AE reports in multi-site trials. The Roundtable's recommendations in this regard are detailed herein.

The Roundtable believes that these recommendations are consistent with the views and recommendations expressed by a number of the stakeholders during the March 21 FDA hearing, including ARENA, PRIM&R, P***h***RMA, and the CIOMS VI Working Group.

The Roundtable looks forward to working with FDA, other government agencies, and interested stakeholders on this critical clinical research issue.

Sincerely,



Maureen Donahue Hardwick

APPENDIX A
DEFINITIONS OF KEY TERMS[12]

Adverse Event (synonym to Adverse Experience): Multiple definitions exist such as those which can be found in the FDA Investigational New Drug (IND) and New Drug Application (NDA) regulations, or the International Conference on Harmonisation (ICH) guidelines. However all definitions include similar concepts. The ICH definition prepared with input from various parties including the World Health Organization (WHO) International Drug Monitoring Center is as follows: "Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product."

- ***External Adverse Event***: In a multi-site trial, an AE that occurs at an institution other than the one for which the IRB is directly responsible. These can include AEs experienced by subjects in entirely separate, but related trials.

- ***Internal Adverse Event***: In a multi-site trial, an AE that is experienced by a subject enrolled in a study at the IRB's own institution, not one of the other sites involved in the trial.

Drug Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC): Formal committees charged with reviewing the accumulating data as the trial progresses to monitor safety, effectiveness, and trial conduct issues in a set of recommendations to the sponsor of the clinical study.

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[12] Although US-specific definitions for many of these terms exist, the definitions included in the International Conference on Harmonisation (ICH) have been preferentially used, as they apply to many multi-site (international) clinical programs. Note also that the following definitions are extracted from guidance documents relevant to drugs or biological products. Medical device definitions and reporting requirements are different (sometimes significantly). However, similar underlying guiding principles can be found in device reporting guidance documents and regulations.

Expedited Adverse Event Report (e.g., IND Safety Reports): According to ICH definitions, all Adverse Drug Reactions that are both serious and unexpected are subject to expedited reporting. The definition according to 21 CFR 312.32 includes "(A) Any adverse experience associated with the use of the drug that is both serious and unexpected; or (B) Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity. " ICH guidance documents include clarification that other observations may fulfill the criteria for expedited reporting. There are situations in addition to single case reports of "serious" adverse events or reactions that may necessitate rapid communication to regulatory authorities; appropriate medical and scientific judgment should be applied for each situation. In general, information that might materially influence the benefit-risk assessment of a medicinal product or that would be sufficient to consider changes in medicinal product administration or in the overall conduct of a clinical investigation represents such situations. Examples include:

- For an "expected" serious ADR, an increase in the rate of occurrence which is judged to be clinically important.
- A significant hazard to the patient population, such as lack of efficacy with a medicinal product used in treating life-threatening disease.
- A major safety finding from a newly completed animal study (such as carcinogenicity).

Expedited reports are mandated to be submitted to regulatory health authorities under defined timeframes and are to be provided in an expeditious manner to Investigators involved in the conduct of the study.

Unanticipated problems involving risks to human subjects or others: This concept, included in US regulations under the "Common Rule" (21 CFR 56.108 & 45 CFR 46.103) is broader than the above concepts of Adverse Event or even Expedited Adverse Event Report, although there is significant overlap.